AR201-12983B

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 1

ROBUST SUMMARIES

FOR

HEXAHYDROPHTHALIC ANHYDRIDE
(85-42-7)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

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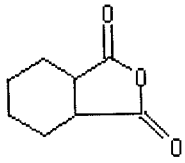
CONTENTS

1. SUBSTANCE INFORMATION

CAS-Number	85-42-7
Name	Hexahydrophthalic Anhydride
Name	**1,3-Isobenzofurandione, Hexahydro-**
EINECS-Number	201-604-9
Molecular Formula	$C_8H_{10}O_3$
Structural Formula	
Other Chemical Identity/Synonyms	1,2-Cyclohexanedicarboxylic acid anhydride; Hexahydro-1,3-isobenzofurandione; Hexahydrophthalic acid anhydride; HHPAA
Molecular Weight	154.16
Type of Substance	element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]
Physical State *(at 20°C and 1.013 hPa)*	gaseous [ ]; liquid [ ]; solid [X]
Purity	**99% weight/weight (approx.)**
SYNONYMS	1,3-Isobenzofurandione, Hexahydro; Cyclohexane-1,2-Dicarboxylic Anhydride; HHPAA

IMPURITIES

CAS No:	1687-30-5 (610-09-3, cis-; 2305-23-0 trans-)
EINECS No:	216-872-2
Name:	Hexahydrophthalic Acid
Value:	0.5% (maximum weight/weight)

Sulfated ash 0.1% max.; potassium 50 ppm max.; sodium 50 ppm max.; traces of tetrahydro PAA, hexahydrobenzoic acid and mixed anhydride
Reference: Buffalo Color Corp., 1/96

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

(a)

Value:	35-37 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

(b)

Value:	34-38 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., HHPA MSDS, 06/06/99

(c)

Value:	37 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, HHPA MSDS, 3/14/95

B. BOILING POINT

(a)

Value:	158 °C
Pressure:	17 mm Hg
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

B. BOILING POINT (continued)

(b)

Value:	144 °C
Pressure:	17 mm Hg
Decomposition:	Yes [ ] No **[X]** Ambiguous **[ ]**
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., HHPA MSDS, 06/06/99

(c)

Value:	285 °C
Pressure:	No Data
Decomposition:	Yes [ ] No **[X]** Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, 1/96

(d)

Value:	296 °C
Pressure:	760 mm Hg
Decomposition:	Yes [ ] No **[X]** Ambiguous **[ ]**
Method:	No Data
GLP:	Yes **[ ]** No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, HHPA MSDS, 03/14/95

C. VAPOR PRESSURE

(a)

Value:	5.00 mm Hg
Temperature:	106 °C
Method:	calculated [ ]; measured **[ ]**; ? **[X]** No Data
GLP:	Yes **[ ]** No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, Tech Data Sheet "Anhydrides"

(b)

Value:	10.00 mm Hg
Temperature:	125 °C
Method:	calculated [ ]; measured [ ] ? **[X]**
GLP:	Yes [ ] No **[ ]** ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

C. VAPOR PRESSURE

(c)

Value:	0.25 mm Hg
Temperature:	30 °C
Method:	calculated **[X]**; measured **[ ]** ? **[ ]**
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	No Data
Reference:	Buffalo Color Corporation, 1/96

(d)

Value:	0.0068 mm Hg
Temperature:	25 °C
Method:	calculated **[X]**; measured **[ ]** ? **[ ]**
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	No Data
Reference:	Dixie Chemical Company, Inc., HHPA MSDS, 06/06/99

D. PARTITION COEFFICIENT $\log_{10}$Pow

Log_{10} Pow:	1.33 ± 0.14
Temperature:	No Data
Method:	calculated **[ ]**; measured **[ ]** ? **[X]**
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	Octanol/Water Partition Coefficient, P=21.4
Reference:	Fuhr, A.B./R.J. Dugan, 1982; Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

E. WATER SOLUBILITY

Value:	Insoluble - Hydrolyzes
Temperature:	No Data
Description:	Miscible**[ ]**; Of very high solubility **[ ]**; Of high solubility **[ ]**; Soluble **[ ]**; Slightly soluble **[ ]**; Of low solubility **[ ]**; Of very low solubility **[ ]**; Not soluble **[X]**
Method:	No Data
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	Hydrolyzes in water or dilute alkali to form diacid or salt. Slowly hydrolyzes in dilute acids. Miscible with benzene, toluene, acetone, carbon tetrachloride, and chloroform. Soluble in methanol.
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96)

F. pH VALUE, pKa VALUE

pH Value:	4.2
Concentration:	1% aqueous mixture
Temperature:	No Data
Method:	Calculated
GLP:	Yes [ ] No [ ] ? [X]
pKa value	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No Data
Reference:	FDRL Report, January 28, 1981

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

Type:	Air
Rate Constant:	0.45 X 10^{-11} cm^3/molecule/sec
Degradation:	50% after 7.2 days
Method:	Calculated. AOP Computer Programs, Vers. 1.53; Syracuse Research Center, 1994
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Half-life refers to 12-hour days
Reference:	IUCLID Data Sheet, 6/9/94. Atkinson, R., Atkinson, R., *A Structure-Activity Relationship for the Estimation of Rate Constants for the Gas-Phase Reactions of OH Radicals With Organic Compounds,* Int. J. Chem. Kinet 19:799-828, 1987.

B. STABILITY IN WATER

Type:	Field trial [ ]; Laboratory [ ]; Other [X]
Half life:	1 minute at 20 °C and pH=5.2
Degradation:	Not specified quantitatively
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Reliability:	[3] Valid with restrictions
Remarks:	Hexahydrophthalic anhydride will hydrolyze to diacid upon contact with water.
Reference:	Buffalo Color Corporation, 1/96

C. BIODEGRADATION

(a)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Concentration:	10 mg/L related to DOC
Medium:	No Data
Degradation:	9.7% after – hours
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	No Data
Results:	Mean retention time of 3 hours
Test Conditions:	No Data
GLP:	Yes **[ ]** No **[X]** ? **[ ]**
Reliability:	[1] Valid without restrictions
Remarks:	None
Reference:	IUCLID Data Sheet, 6/9/94. Huels, *Unpublished Data*

(b)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Chemical concentration:	100 mg/L
Medium:	No Data
Degradation:	No Data
Kinetics:	No Data
Method:	*Method for Testing the Biodegradability of Chemical Substances by Microorganisms,* stipulated in *Testing Methods for New Chemical* Substances (July 13, 1974). Essentially the same test as in OECD Guidelines for Testing of Chemicals for Ready Biodegradability OECD Guideline 303A: Modified MITI Test (I) Guideline #301C, July 17, 1992.
Test Substance:	HHPA – 100% purity
Results:	Biodegradation (as measured by BOD) ranged from 1-6% at the end of the 28 day period in the three replicate tests. The percentage TOC ranged from 1-5% in the three test solutions at the end of the 28 day period. At the termination of cultivation, insoluble compound was not observed and sludge growth was not observed.
Test Conditions:	Concentration of test substance was 100 mg/L. Concentration of activated sludge was 30 mg/l (as the concentration of suspended solid). Volume of test solution was 300 ml. Cultivation temperature was 25 °C and cultivation duration was 28 days. Change in BOD was measured continuously. The pH of the test solutions (sludge and test substance) was adjusted to pH 7 initially and was pH 7 at the end of the cultivation period. The pH of the control vessel (test substance dissolved in water) was 3.9 at the end of the 28 day period.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Reliability:	[1] Valid without restrictions
Remarks:	The percent biodegradation in the three test solutions as measured by BOD and TOC were as follows: Vessel 1 – 1% BOD, 5% TOC; Vessel 2 – 2% BOD, 1% TOC; and Vessel 3 – 6% BOD, 3% TOC. At the end of cultivation, insoluble compound and sludge growth were not observed in the test vessels. In the control solution, insoluble compound was not observed at the end of the 28 day period.
Reference:	Karume Laboratory, Chemicals Evaluation and Research Institute, Japan. *Unpublished Report*; May, 1985.

D. BOD_5,COD OR RATIO BOD_5/COD

ThOD:	1.87 g O_2/g
Method:	Calculated
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corp., 1/96

E. TRANSPORT AND DISTRIBUTION

No data.

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

(a)

Type of Test:	Static
Species/strain:	*Oryzias latipes* (Ricefish)
Exposure period:	48 Hours
Results:	LC_{50}: > 500 mg;/L (estimated by Duodoroff Method)
Temperature:	25 ± 2 °C
Method:	Japanese Industrial Standard (JIS K 0102-1998-71), *Testing Methods for Industrial Waste Water/ Acute Toxicity Test with Fish.*
Test Substance:	Cis-1,3-cyclohexanedicarbosylic acid @ 98% purity.
Analytical Monitoring:	Yes **[X]**; No [ ]
Remarks:	Test conditions: Volume of test water was 4 L. Temperature of water was 25 ± 2 °C. Concentration of dissolved oxygen was 7.3 mg/L initially and final concentration was 4.3 mg/L. Ten (10) fish were used per level.
GLP:	Yes **[X]** No [ ] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	Karume Laboratory, Chemicals Evaluation and Research Institute, *Unpublished Report*, December 1985.

(b)

Type of Test:	Static
Species/strain:	*Leuciscus idus,* (Freshwater fish)
Exposure period:	48 Hours
Results:	LC_{50}: 660 mg/L
Temperature:	No Data
Method:	Bestimmung dur Wirken von Wasserinhaltstoffe Auf Fischz, DIN 38412 Teilij
Test Substance:	No Data
Analytical Monitoring:	Yes [ ]; No **[X]**
Remarks:	None
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	IUCLID Data Sheet, 6/9/94. Huels, *Unpublished Data,* 1983.

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

Type of Test:	Static
Species/strain:	*Daphnia magna*
Exposure period:	24 Hours
Results:	EC_{50} = 103 mg;/L
Temperature:	No Data
Method:	Daphnien-Kurzzeit Test, DIN 38412, Teel 11, Bestimmung der Wirking von Wasserunhalt-Staffe auf Kleinkrebse
Test Substance:	No Data
Analytical Monitoring:	Yes [ ]; No [X]
Remarks:	None
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	IUCLID Data Sheet, 6/9/94. Huels-Bericht, A.W., 147; *Unpublished Data,* 1988.

C. TOXICITY TO AQUATIC PLANTS - ALGAE

Type of Test:	No Data
Species/strain:	*Scenedesmus suspicatus,* (Algae)
Exposure period:	72 Hours
Results:	EC_{10}: 54 mg;/L; EC_{50}: 95.6 mg/L; EC_{90}: 169.4 mg/L
Temperature:	No Data
Method:	Algeniruchstums-Hemin Test nach UBA, 1984
Test Substance:	No Data
Analytical Monitoring:	No Data
Remarks:	Endpoint – growth rate
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	IUCLID Data Sheet, 6/9/94. Huels-Bericht, A.W., 147; *Unpublished Data,* 1988.

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley rats
Value:	2700-2800 mg/kg (estimated, see Remarks)
Method:	5 rats/sex at doses of 1500, 2027, 2739, 3700 and 5000 mg/kg. Body weights were checked on days 1, 8 and 15. Daily observations and gross autopsies were conducted.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	25% TS (w/w) in corn oil slurry
Remarks:	Decreased activity and/or urinary incontinence were seen at all doses. Survivors had normal weight gains for 14 days post exposure. Mortality rates were 0 of 5 males and 1 of 5 females at 1500 mg/kg; 0 of 5 males and 0 of 5 females at 2027 mg/kg; 2 of 5 males and 3 of 5 females at 2739 mg/kg; 5 of 5 males and 4 of 5 females at 3700 mg/kg; and 5 of 5 males and 5 of 5 females at 5000 mg/kg. Necropsy was unremarkable in survivors. Decedents showed blood-like liquid, primarily in the intestines.
Reliability:	[2] Valid with restrictions
Reference:	Food and Drug Research Laboratory, 1981.

(1) ACUTE ORAL TOXICITY (continued)

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Value:	3307 mg/kg
Method:	No Data
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Remarks:	Moderately toxic. Limited data on doses and number of animals
Reliability:	[3] Not valid
Reference:	Oral report from Syracuse University Research Institute, 1980.

(2) ACUTE INHALATION TOXICITY

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [X]; LCL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley rats
Exposure time:	4 hours
Value:	LC_{50} > 1100 mg/m^3 (aerosol)
Method:	A group of five(5) male and five(5) female rats were exposed for 4 hours to an aerosol of an 80% (w/w) solution in ethanol – a maximum attainable concentration. Rats were observed daily. Body weights were taken on days 3, 4, 5, 8 and 15 post-exposure. Necropsies were done at termination.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	80% (w/w) solution in ethanol
Remarks:	All rats survived and necropsies were unremarkable. Decreased activity was seen during exposure and body weights were depressed during the first week, followed by recovery in second week. Particle size was a geometric mean size of 5.8 μm (GSD = 2.2). Seventy-five (75) percent of the particles were less than 10 μm indicating a respirable aerosol.
Reliability:	[2] Valid with restrictions
Reference:	Food and Drug Research Laboratory, Study No. 6771H, 1981.

(3) ACUTE DERMAL TOXICITY

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	New Zealand albino rabbits
Value:	LD_{50} > 2000 mg/kg
Method:	Limit test (OECD modification). Five male and five female rabbits were dosed with the solid material at 2000 mg/kg body weight on abraded skin, under a porous gauze dressing, for 24 hours and then observed for 14 days. Body weights were taken on days 1, 8 and 15 and gross autopsies were done at termination.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Solid material – unknown purity
Remarks:	No rabbits died and no gross signs were seen except minimal irritation on day 2. Gross autopsy at termination was unremarkable.
Reliability:	[2] Valid with restrictions
Reference:	Food and Drug Research Laboratory Study No. 6771 H, 1981.

B. REPEATED DOSE TOXICITY (General)

(a)

Species/strain:	Mice
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data **[X]**
Route of Administration:	Intraperitoneal
Exposure period:	8 days
Frequency of treatment:	No Data
Post exp. observation period:	No Data
Dose:	500 mg/kg/day
Control group:	Yes [ ]; No [ ]; No Data **[X]**; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	No Data
LOEL:	No Data
Results:	6 out of 6 "tumor bearing" mice survived 500 mg/kg x 8 days with no toxic signs reported.
Method:	No Data
GLP:	Yes [ ]; No [ ]; ? **[X]**
Test substance:	Comments: None
Reliability:	[3] Not valid
Reference:	Southern Research Laboratory Report NSC 8622 to CGNSC, 2/21/57.

(b)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data **[X]**
Route of Administration:	Gavage
Exposure period:	300 days
Frequency of treatment:	5 days/week
Post exp. observation period:	No Data
Dose:	330 mg in olive oil/kg/day (10 animals/group)
Control group:	Yes [ ]; No [ ]; No Data **[X]**; Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
NOEL:	No Data
LOEL:	No Data
Results:	5 out of 10 rats survived over 300 days at a feeding level of 330 mg/kg/day in olive oil. (2 killed by accident) No information on body weight, toxic signs or pathology.
Method:	No Data
GLP:	Yes [ ]; No [ ]; ? **[X]**
Test substance:	Comments: None
Reliability:	[3] Not valid.
Reference:	Letter: Ferber, K. H./B. M. Helfaer, 1957. Re: Syracuse U. Res. Inst. Oral Report, Item 5.0.21, 12/16/57.

C. GENETIC TOXICITY IN VITRO

(a)

BACTERIAL

Type:	Bacterial reverse mutation assay (Ames test)
Species/strain:	*Salmonella typhimurium* bacteria (Strains TA98, TA100, TA1535, TA1537, and TA 1538)
Test System:	Standard plate method
Concentration:	Up to 1000 µg/plate
Metabolic Activation:	With **[X]**; Without **[X]**
Results:	Not mutagenic
Cytotoxic Concentration:	No Data
Precipitation:	No Data
Genotoxic Effects:	Negative with and without metabolic activation
Method:	Standard Ames test as cited in *Mutation Research* 31:347-364, 1975.
GLP:	Yes [ ] No **[X]** ? [ ]
Test substance:	No Data
Remarks:	None.
Reliability:	[2] Valid with restrictions.
Reference:	IUCLID Data Sheet, 6/9/94. Huels Report No. 7923, *Unpublished Data,* 1979.

(b)

NON-BACTERIAL *IN VITRO* TEST (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

Type:	Dermal Irritation/Corrosivity
Species/strain:	New Zealand albino rabbits
Results:	Highly corrosive **[ ]**; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating **[X]**; Not irritating **[ ]**
Classification:	Highly corrosive (causes severe burns) **[ ]**; Corrosive (caused burns) [ ]; Irritating **[X]**; Not irritating [ ]
Method:	Draize test. Application of 0.5 ml of various solutions to each of 6 rabbits with scoring at 24 and 72 hours.
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	Concentrations of 6.25, 12.5, 25, and 50% in mineral oil
Remarks:	Minimal to slight irritation was seen at $\leq$ 50%. Classified as "irritating" in accordance with EC Directive 6/548/EEC. Primary irritation scores were: 0.17 at 6.25%; 0.67 at 12.5%; 0.58 at 25%; and 0.92 at 50% (0.92 = minimal to slight irritation). Mineral oil alone scored 0.42.
Reliability:	[2] Valid with restrictions
Reference:	Food Drug Research Laboratory, Study No. 7232H, 1982.

(2) EYE IRRITATION/CORROSION

(a)

Type:	OECD (Irrigation and non-irrigation)
Species/strain:	New Zealand albino rabbits
Results:	Highly corrosive [ ]; Corrosive **[X]**; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not irritating **[ ]**; Risk of serious damage to eyes **[X]**
Method:	Draize Test. One hundred (100) mg of solid material was applied to 6 rabbits without irrigation and to 3 rabbits each for irrigation at either 4 or 30 seconds. Irritant effects were scored up to 21 days.
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	Undiluted solid
Remarks:	HHPA may cause "Risk of Serious Damage to Eyes" in accordance with EC Directive 67/543/EEC. Unwashed eyes and those washed at 30 seconds showed severe irritation and corrosion with no recovery at 21 days. Rabbits irrigated at 4 seconds showed severe but reversible irritation by 19 days.
Reliability:	[2] Valid with restrictions.
Reference:	FDRL Report of Study 6771-H, February 27, 1981

(b)

Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating **[X]**; Slightly irritating [ ]; Not irritating **[ ]**
Classification:	Irritating **[X]**; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method:	Draize Test
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	No Data
Reliability:	[3] Not valid
Remarks:	Washout after 4 seconds. Score of 39 on a Draize scale of 110 at 24 hours was reported.
Reference:	FDRL Report of Study 6771-H, February 27, 1981

(c)

Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating **[X]**; Irritating **[ ]**; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating **[X]**; Not irritating [ ]; Risk of serious damage to eyes [ ]
Method:	Draize Test
GLP:	Yes [ ] No [ ] ? **[X]**
Test substance:	Comments: None
Reliability:	[3] Not valid
Remarks:	Washout after 30 seconds. 86 on a Draize scale of 110 at 13 days.
Reference:	FDRL Report of Study 6771-H, February 27, 1981

B. SKIN SENSITIZATION

Type:	
Species/strain:	Human
Results:	Sensitizing **[X]**; Not sensitizing **[ ]**; ambiguous **[ ]**
Classification:	Sensitizing **[X]**; Not sensitizing **[ ]**
Method:	No Data
GLP:	Yes **[X]** No **[ ]** ? **[ ]**
Test substance:	5% suspension HHPAA in mineral oil (10 repeat test). None
Reliability:	[2] Valid with restrictions
Remarks:	Four out of fifty-three subjects gave a low grade sensitivity reaction and one marked reaction indicating sensitization.
Reference:	Buffalo Color Corporation, MSDS 127-2639 (9/11/96); FDRL Report of Study OE No. 2471, May 7, 1982.

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. All of the anhydrides within the cyclic anhydride category are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were located for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

Manufacturers of HHPA have not reported significant adverse effects on worker health but exposure levels are unknown. Transient effects (skin, eye, and respiratory tract irritation) have been noted as well as general signs like anemia, headache, fever and dizziness. Hypersensitivity effects have also been reported and include asthma, urticaria, contact dermatitis, fever, chills, hemolysis and respiratory sensitizations. Several key studies are subsequently summarized.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

(a)

Method:	A questionnaire, lung function, and blood tests were given to HHPA exposed workers to determine the presence of immunoglobulin-E(IgE) and immunoglobulin-G (IgG) antibodies against hexahydrophthalic human serum albumin (HHP-HSA). The 57 workers who reported symptoms or demonstrated specific antibodies were skin tested with HHP-HSA and interviewed and examined by a physician.
Results:	Sixteen of the 57 were found to have IgE mediated disease and seven had both IgE and IgG mediated disease.
Reliability:	[2] Valid with restrictions
Remarks:	IgE and IgG antibody status were found to be significant positive predictors for IgE and IgG disease respectively. The authors concluded that development of following exposure to HHPA, the development of immunologically mediated respiratory disease is most closely associated with development of IgE or IgG antibodies to HHP-HSA and exposure level. After the workers were removed from exposure for 1 year, no symptoms, physical findings, spirometry or chest x-rays indicated permanent damage due to HHPAA-induced respiratory disease; however, both serum IgE and IgG for HHPAA persisted in the workers after 1 year.
Reference:	Grammer, L.C., et al., 1994; Grammer, L. C., 1995

C. RESPIRATORY SENSITIZATION (continued)

(b)

Method: Historical data

Results: Source: Buffalo Color Corporation
No serious incidents, case reports, or other epidemiology was noted in workers exposed to HHPAA.

Reliability: [4] Not assignable

Remarks: Manufactured by Buffalo Color Corporation for a number of years without reported significant adverse effects on health but early exposure levels are unknown. There have been cases of transient irritation.

Reference: Buffalo Color Corporation, Occupational and Environmental Health Hazard Summary and Evaluation of Commercial Grade Chemicals, Issue No. 4, pg. 12, Date: 12/95.

(c)

Method: In a cross-sectional study on 95 workers in two plants which used HHPA as a hardener for epoxy resin the radio allergo sorbent test (RAST) and enzyme linked immunosorbent assay were used to determine antibody levels to IgE and IgG respectively. The mean time of exposure was 7 hours (range 0.1-25) years.

Results: The specific IgE and IgG levels were significantly increased in workers as compared with external referents or unexposed workers.

Reliability: [2] Valid with restrictions

Remarks: Study indicates that short-time peak exposures may affect IgE sensitization and HHPA can cause sensitization even at low levels.

Reference: Welinder, H.E., et al., 1994.

(d)

Method: Nasal challenge tests were performed with a conjugate of HHPA and human serum albumin (HAS) at three increasing concentrations in exposed workers to test the pathogenetic relevance of serum antibodies (IgE and IgG).

Results: Eleven subjects who reported work-related nasal symptoms and were IgE-sensitized against HHPA (Positive in skin-prick test and RAST against HHPA-HAS conjugate) had a decrease of nasal inspiratory peak flow and a significant increase of symptoms after the challenges. Eleven unsensitized subjects with no symptoms and nine unsensitized subjects who complained of work-related nasal symptoms displayed no significant change in any parameter.

Reliability: [2] Valid with restrictions

Remarks: The authors concluded that symptoms in some of the workers were caused by an IgE-mediated mast cell degranulation and ensuing inflammatory reaction involving eosinophil and neutrophil cells.

Reference: Neilsen, J., et al., 1994

(e)

Method: Results from a radio allergo sorbent test (RAST) and skin prick test (using 1% and 5% acetonic solution) of commercially available phthalic anhydride were compared to results from RAST and skin prick tests using the not commercially available conjugates of HHPA and MTHPA. 110 employees exposed to HHPA and MTHPA were examined using the PA conjugates and 109 of the 110 were examined using HHPA and MTHPA conjugates.

Results: Specific IgE against acid anhydrides was detected in a total of 17 persons and 6 sensitizations in the challenge test were clinically relevant. The PA conjugate RAST produced three false negatives and one false positive when compared with a RAST using HHPA and MTHPA conjugates when borderline positive findings using the PA conjugate RAST were included. In comparison with the RAST, the skin prick test gave three false positive and three false negative results.

Reliability: [2] Valid with restrictions

Remarks: The authors concluded that RASTs with conjugates of PA and skin prick tests with native acid anhydrides can validly ascertain workplace-related sensitizations to HHPA and MTHPA.

Reference: Drexler, H., et al., 1994

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 2

ROBUST SUMMARIES

FOR

TETRAHYDROPHTHALIC ANHYDRIDE
(85-43-8)

Submitted to the U.S. EPA

By

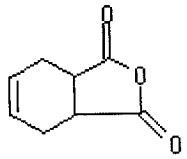
The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

March, 2001

CONTENTS

1. GENERAL INFORMATION

CAS-Number	85-43-8
Name	4-Cyclohexene-1,2-dicarboxylic anhydride
CAS Descriptor	Not Applicable
EINECS-Number	201-605-4
Molecular Formula	$C_8O_8O_3$
Structural Formula	
Other Chemical Identity/Synonyms	4-Cyclohexene-1,2-dicarboxylic acid, anhydride (cis); Tetrahydrophthalic anhydride; 1,2,3,6-Tetrahydrophthalic anhydride; THPA
Type of Substance	element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]
Physical State *(at 20°C and 1.013 hPa)*	gaseous [ ]; liquid [ ]; solid [X]
Purity	>99% weight/weight (approx.)
SYNONYMS	4-Cyclohexene-1,2-dicarboxylic acid, anhydride (cis); THPA

IMPURITIES

No Data

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

(a)

Value:	99 °C (210 °F) minimum
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, MSDS (8/13/98)

A. **MELTING POINT (continued)**

(b)

Value:	102 °C (216 °F) minimum
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(c)

Value:	100 °C (212 °F) minimum
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	EUCLID Data Sheet, 1994

B. **BOILING POINT**

(a)

Value:	195 °C
Pressure:	50 mm Hg
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[3] Not valid
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(b)

Value:	195 °C
Pressure:	1013 hPa
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[3] Not valid
Remarks:	None
Reference:	EUCLID Data Sheet, 1994

C. VAPOR PRESSURE

(a)

Value:	<0.01 mm Hg
Temperature:	20 °C
Method:	calculated **[X]**; measured **[ ]**; ? **[ ]**
	No Data
GLP:	Yes [ ] No **[X]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Co., Inc., MSDS (8/13/98)

(b)

Value:	0.01 mm Hg
Temperature:	20 °C
Method:	calculated [ ]; measured **[ ]**; ? **[X]**
	No Data
GLP:	Yes **[ ]** No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

(c)

Value:	50.0 mm Hg
Temperature:	195 °C
Method:	calculated **[X]**; measured [ ]; ? [ ]
	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Co., Inc., MSDS (8/13/98)

D. PARTITION COEFFICIENT $\log_{10}$Pow

Log_{10}Pow:	0.02
Temperature:	No Data
Method:	calculated **[X]**; measured [ ]; ? [ ]
GLP:	Yes [ ]; No [ ]; ? **[X]**
Reliability:	[3] Not valid
Remarks:	None
Reference:	EUCLID Data Sheet, 1994; Hansch, L. *Berechnung mit dem MedChem-Programm*, Version 1989 (POMONA89)

E. WATER SOLUBILITY

(a)

Value:	10 g/l
Temperature:	20 °C
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble **[X]**; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[3] Not valid
Remarks:	Slowly hydrolyzes to diacid in water.
Reference:	EUCLID Data Sheet, 1994; Huels, A.G., Sicherheitsdatenblatt, 10/1/93

(b)

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble **[X]**
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[3] Not valid
Remarks:	Slowly hydrolyzes to diacid in water.
Reference:	Dixie Chemical Co., Inc., MSDS (8/13/98)

(c)

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble **[X]**; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[3] Not valid
Remarks:	Slightly soluble with hydrolysis.
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

F. pH Value, pKa Value

(a)

pH Value:	2.1
Concentration:	1 g/l
Temperature:	20 °C
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
PKa Value:	No Data
Reliability:	[3] Not valid
Remarks:	No Data
Reference:	Lonza Inc./Lonza Spa, MSDS 4445 THPA (3/14/95)

F. **pH Value, pKa Value (continued)**

(b)

pH Value:	2.1
Concentration:	10 g/l
Temperature:	No Data
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
PKa Value:	No Data
Reliability:	[3] Not valid
Remarks:	No Data
Reference:	EUCLID Data Sheet, 1994; Huels, A.G., Sicherheitsdatenblatt, 10/1/93

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Remarks: Slowly hydrolyzes to diacid.

C. BIODEGRADATION

(a)

Type:	Aerobic [X]; Anerobic [ ]
Innoculum:	Activated sludge
Concentration:	100 mg/L (test substance)
Medium:	No Data
Degradation:	0.0%
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	Tetrahydrophthalic anhydride (Purity unknown)
Results:	Zero percent biodegradation as measured by BOD.
Test Conditions:	Three replicate tests were conducted. Concentration of the test substance was 100 mg/L. The activated sludge concentration was 30 mg/L. The volume of the test solution was 300 ml. A constant temperature of 25 °C was maintained for 28 days.
GLP:	Yes [X]; No [ ]; ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	Biochemical Oxygen Demand (BOD) was determined to calculate percent biodegradation.
Reference:	Report cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992.

C. BIODEGRADATION (continued)

(b)

Type:	Aerobic [X]; Anerobic [ ]
Innoculum:	Predominantly domestic sewage
Concentration:	10 mg/l related to DOC (Dissolved Organic Carbon)
Medium:	No Data
Degradation:	21% after 21 days
Kinetics:	No Data
Method:	OECD Guideline 301E, *Ready Biodegradability: Modified OECD Screening Test*
Test Substance:	'As prescribed by 1.1-1.4'
Results:	No Data
Test Conditions:	No Data
GLP:	Yes [ ]; No [X]; ? [ ]
Reliability:	[1] Valid without restrictions
Remarks:	None
Reference:	EUCLID Data Sheet, 1994; Huels-Untersuchung (unveroeffentlict), 1981

D. TRANSPORT AND DISTRIBUTION

No Data

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

Type of test:	Static
Species/strain:	*Leuciscus idus,* (freshwater species)
Exposure period:	48 hours
Results:	LC_{50}: 610 mg/l
Temperature:	'As prescribed by 1.1-1.4'
Method:	Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15
Test Substance:	No Data
Analytical monitoring:	Yes [ ] No [X] ? [ ]
Remarks:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions.
Reference:	EUCLID Data Sheet, 1994; Huels-Untersuchung, 1983 (unveroeffentlicht)

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

Type of test:	No Data
Species/strain:	*Daphnia magna* (Crustacea)
Exposure period:	24 hours
Results:	EC_{50}: 117 mg/l
Temperature:	No Data
Method:	Daphnien-Kurzzeittest, DIN 38412 Teil 11, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse
Test Substance:	'As prescribed by 1.1-1.4'
Analytical monitoring:	Yes [ ] No [X] ? [ ]
Remarks:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	EUCLID Data Sheet, 1994; Huels-Bericht D324, 1988 (unveroeffentlicht)

C. TOXICITY TO AQUATIC PLANTS - ALGAE

Type of test:	No Data
Species/strain:	*Scenedesmus subspicatus* (Algae)
Exposure period:	72 hours
Results:	EC_{10}: 45.4 mg/l; EC_{50}: 65.7 mg/l; EC_{90}: 95.2 mg/l
Temperature:	No Data
Method:	Algenwachstums-Hemmtest nach UBA (Verfahrensvorschlag Stand Februar 1984)
Test Substance:	'As prescribed by 1.1-1.4'
Analytical monitoring:	Yes [ ] No [X] ? [ ]
Remarks:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions.
Reference:	EUCLID Data Sheet, 1994; Huels-Bericht, A.W., 1988 (unveroeffenlicht)

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	3 g/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Reliability:	[4] Not assignable
Remarks:	No specifics reported other than the lethal dose. Route of exposure was unreported.
Reference:	RTECS, 1999; Gig. Trud. Prof. Zabol. 29(12):37, 1985

(1) ACUTE ORAL TOXICITY (continued)

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Mouse
Value:	3300 mg/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Remarks:	No specifics reported other than the lethal dose. Route of exposure was unreported.
Reliability:	[4] Not assignable
Reference:	RTECS, 1999; Gig. Trud. Prof. Zabol. 29(12):37, 1985

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Guinea Pig
Value:	3500 mg/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Remarks:	No specifics reported other than the lethal dose. Route of exposure was unreported.
Reliability:	[3] Not valid
Reference:	RTECS, 1999; Gig. Trud. Prof. Zabol 29(12):37, 1985

(d)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	5410 mg/kg (4590-6380 mg/kg)
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	No details reported.
Reliability:	[4] Not assignable
Reference:	EUCLID Data Sheet, 1994; Marhold, J.V. Institut Prov Vychova Vedoucin Pracovniku Chemikeho Prymyelo Praha, p. 140, 1972

(2) ACUTE INHALATION TOXICITY

No Data

(3) ACUTE DERMAL TOXICITY

No Data

B. REPEATED DOSE TOXICITY (General)

No Data

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

Type:	Bacterial reverse mutation assay (Ames test)
Species/strain:	*Samonella typhimurium* (Strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538)
Test System:	Standard plate method
Concentration:	1000 µg/ plate (maximum concentration)
Metabolic Activation:	With **[X]**; Without **[X]**
Results:	Negative
Cytotoxic Concentration:	No Data
Precipitation:	No Data
Genotoxic Effects:	Negative with and without metabolic activation.
Method:	Standard Ames test as cited in *Mutation Research* 31:347-364, 1975.
GLP:	Yes [ ] No **[X]** ? [ ]
Test Substance:	' As prescribed by 1.1-1.4'
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 7924, 1979 (unpublished)

(2) NON-BACTERIAL *IN VITRO* TEST (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

(a)

Type:	Dermal Irritation/Corrosivity
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating **[X]**; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating **[X]**; Not Irritating [ ]
Method:	Draize test
GLP:	Yes [ ] No [ ] ? **[X]**
Test Substance:	No Data
Reliability:	[3] Not valid
Remarks:	500 mg was applied over a 24 hour time period.
Reference:	RTECS, 1999; Prehled Prumyslove Toxikologie, Organicke Latky, Masrhold, J., pg. 322, 1986.

(1) SKIN IRRITATION/CORROSION (continued)

(b)

Type:	Dermal Irritation/Corrosivity
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [X]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [ ]; Not Irritating [X]
Method:	Draize test.
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	'As prescribed by 1.1-1.4'
Reliability:	[2] Valid with restrictions
Remarks:	Irritation index: 0, 6/8 Redness: x=0,44 (EEC Annex VI) Edema: x=0
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1271, 1988 (unpublished)

(2) EYE IRRITATION/CORROSION

(a)

Type:	Acute Eye Irritation/Corrosion
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [X]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not Irritating [ ]; Risk of serious damage to eyes [X]
Method:	OECD Guideline 405, *Acute Eye Irritation/Corrosion,* 1981
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No scores were calculated since only one animal used in the test. The test was stopped after one hour due to the possible risk of irreversible effects.
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1272, 1988 (unpublished)

(b)

Type:	Draize
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [X]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [X]; Not Irritating [ ]; Risk of serious damage to eyes [ ]
Method:	Draize test
GLP:	Yes [ ] No [ ] ? [X]
Test Substance:	No Data
Reliability:	[3] Not valid
Remarks:	Application of 20mg produced moderate irritation at 24 hours.
Reference:	RTECS, 1999; Prehled Prumyslove Toxikologie; Organicke Latky, Marhold, J., pg. 322, 1986

(1) SKIN IRRITATION/CORROSION (continued)

(b)

Type:	Dermal Irritation/Corrosivity
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [X]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [ ]; Not Irritating [X]
Method:	Draize test.
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	'As prescribed by 1.1-1.4'
Reliability:	[2] Valid with restrictions
Remarks:	Irritation index: 0, 6/8 Redness: x=0,44 (EEC Annex VI) Edema: x=0
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1271, 1988 (unpublished)

(2) EYE IRRITATION/CORROSION

(a)

Type:	Acute Eye Irritation/Corrosion
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [X]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not Irritating [ ]; Risk of serious damage to eyes [X]
Method:	OECD Guideline 405, *Acute Eye Irritation/Corrosion,* 1981
GLP:	Yes [ ] No [X] ? [ ]
Test Substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No scores were calculated since only one animal used in the test. The test was stopped after one hour due to the possible risk of irreversible effects.
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1272, 1988 (unpublished)

(b)

Type:	Draize
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly Irritating [ ]; Irritating [ ]; Moderate irritating [X]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [X]; Not Irritating [ ]; Risk of serious damage to eyes [ ]
Method:	Draize test
GLP:	Yes [ ] No [ ] ? [X]
Test Substance:	No Data
Reliability:	[3] Not valid
Remarks:	Application of 20mg produced moderate irritation at 24 hours.
Reference:	RTECS, 1999; Prehled Prumyslove Toxikologie; Organicke Latky, Marhold, J., pg. 322, 1986

B. SKIN SENSITIZATION

Type:	Guinea Pig Maximization Test
Species/stain:	Guinea Pig
Results:	Sensitizing **[X]**; Not Sensitizing [ ]; ambiguous [ ]
Classification:	Sensitizing **[X]**; Not Sensitizing [ ]
Method:	OECD Guideline 406 *Skin Sensitization*, 1981
GLP:	Yes [ ] No **[X]** ? [ ]
Test Substance:	'As prescribed by 1.1-1.4'
Reliability:	[2] Valid with restrictions.
Remarks:	Seventeen (17) of the 20 guinea pigs showed a positive response.
Reference:	EUCLID Data Sheet, 1994; Huels Report No. 1218, 1988 (unpublished)

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were located for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

Method:	Guinea pigs were immunized intradermally with a single dose of 0.3 M solution of THPA and other anhydrides. Specific IgE and IgG antibodies specific for guinea-pig serum albumin conjugates of the anhydrides were determined by passive cutaneous anaphylaxis (PCA) tests and enzyme-linked immunoabsorbant assay (ELISA).
Results:	Specific IgG levels were increased in only three (3) of nine (9) animals immunized with THPA. Less than 10% of the animals in the THPA immunized group were positive for specific IgE antibodies.
Reliability:	[2] Valid with restrictions
Remarks:	Specific IgG, totals were analyzed by ELISA assay. PCA was used for analysis of IgE. It should be noted that the PCA assay has low sensitivity and may not detect low titer levels of antibody. Product purity was $\geq$ 97%. The primary purpose of this article was to investigate structure activity relationships of organic acid anhydrides. The authors concluded that substitution of a hydrogen atom for a methyl group enhanced antibody formation. This substitution appeared to be the most marked general effect of chemical structure on immunogenicity.
Reference:	Welinder, H., et al., 1995

7. REFERENCES

Dixie Chemical Co., Inc., *Material Safety Data Sheet – Tetrahydrophthalic Anhydride,* 8/13/98

EUCLID Data Sheet (Lonza Inc.), Creation Date: 09/06/93; Revision Date: 01/11/94

Grammer, L. C. et al., *Hemorrhagic Rhinitis – An Immunologic Disease due to Hexahydrophthalic Anhydride*, Chest 104(6):1792-1794, 1993

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Japan Chemical Industry Ecology-Toxicology Information Center, *Cited Report Summary*, October, 1992

Kanerva, L. et al., *Delayed and Immediate Allergy caused by Methylhexahydrophthalic Anhydride*, Contact Dermatitis 36(1):34-38, 1997

Kanerva, L. et al., *Airborne Allergic Contact Urticaria from Methylhexahydrophthalic Anhydride and Hexahydrophthalic Anhydride* Contact Dermatitis 41(6):339-341, 1999

Klimisch, H. J., et al., *A systematic Approach for Evaluating the Quality of Experimental and Ecotoxicological Data,* Regulatory Toxicol. & Pharmacol. 25:1-5, 1997.

Lonza Inc./Lonza Spa, *Material Safety Data Sheet 4445 – Tetrahydrophthalic Anhydride,* 3/14/95

RTECS Database, 1999

Welinder, H., et al., *Specific Antibodies to Methyltetahydrophthalic Anhydride in Exposed Workers,* Clin. Exp. Allergy 20(6):639-646, 1990.

Welinder, H. and Nielsen, J., *Immunologic Tests of Specific Antibodies to Organic Acid Anhydrides*, Allergy 46:601-609, 1991

Welinder, H. E. et al., *Exposure-Response Relationships in the Formation of Specific Antibodies to Hexahydrophthalic Anhydride in Exposed Workers*, Scand. J. Work Environ. Health 20(6):459-465, 1994

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 3

ROBUST SUMMARIES

FOR

METHYLHEXAHYDROPHTHALIC ANHYDRIDE
(25550-51-0)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

March, 2001

CONTENTS

1 SUBSTANCE INFORMATION

CAS-Number 25550-51-0

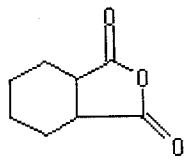
Name Methyl Hexahydrophthalic Anhydride

Name 1,3-Isobenzofurandione, Hexahydro-5-methyl-

EINECS-Number 247-094-1/243-072-0

Molecular Formula $C_9H_{12}O_3$

Structural Formula



D1-Me

Other Chemical Identity/Synonyms Hexahydromethyl-1,3-Isobenzofurandione; MHHPA; Hexahydromethyl- 1,2-Cyclohexane-dicarboxylic anhydride; 5-methyl hexahydro-1,3-isobenzofurandione; Hexahydro-4-Methylphthalic anhydride

Molecular Weight 168

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [ ]; solid [ ]

Purity 99% weight/weight (approx.) – Lonza Group
>99% weight/weight (approx.) – Dixie Chemical Company

SYNONYMS

IMPURITIES

No Data

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

Value:	-30 °C
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

B. BOILING POINT

(a)

Value:	290 °C
Pressure:	No Data
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

(b)

Value:	145 °C
Pressure:	3 mm Hg
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No **[X]** ? [ ]
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS (5/6/99)

C. VAPOUR PRESSURE

(a)

Value:	5.00 mm Hg
Temperature:	137 °C
Method:	calculated [ ]; measured [ ]; ? **[X]**
	No Data
GLP:	Yes [ ] No [ ] ? **[X]**
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

C. VAPOUR PRESSURE (continued)

(b)

Value:	3.00 mm Hg
Temperature:	145 °C
Method:	calculated [ ]; measured [X]; ? [ ]
	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS (5/6/99)

D. PARTITION COEFFICIENT $\log_{10}$Pow

No Data

E. WATER SOLUBILITY

(a)

Value:	<0.1% - Hydrolyzes
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [ ]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	Hydrolyzes in water.
Reference:	Lonza Inc./Lonza Spa, MHHPA MSDS, 3/31/95

(b)

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [ ]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[4] Not assignable
Remarks:	Reacts slowly with water.
Reference:	Dixie Chemical Company, Inc., MSDS (5/6/99)

(c)

Value:	36 g/L
Temperature:	20 °C
Description:	Miscible[ ]; Of very high solubility [ ];
	Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ];
	Of low solubility [ ]; Of very low solubility [ ]; Not soluble [ ]
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[4] Not assignable
Remarks:	None
Reference:	None
Reference:	HEDSET Data Sheet, 1995

F. **pH Value, pKa Value**

No Data

3. **ENVIRONMENTAL FATE AND PATHWAYS**

A. **PHOTODEGRADATION**

No Data

B. **STABILITY IN WATER**

Slowly hydrolyzes to diacid.

C. **BIODEGRADATION**

(a)

Type:	Aerobic [**X**]; Anaerobic [ ]
Inoculum:	Activated Sludge
Concentration:	100 mg/L (test substance)
Medium:	No Data
Degradation:	0.0 %
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	Methyhexahydrophthalic anhydride (Purity unknown)
Results:	Zero percent biodegradation as measured by BOD. Three replicate tests were run. MHHPA was hydrolyzed to corresponding acid.
Test Conditions:	Test substance concentration was 100 mg/L. Activated sludge concentration was 30 mg/L with a test solution volume of 300 ml. Temperature was maintained at 25 °C and cultivation duration was 28 days.
GLP:	Yes [X] No [ ] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Report summary cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992.

D. **TRANSPORT AND DISTRIBUTION**

No Data

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

Type of Test:	Semi-static (test water renewed at 24 hours)
Species/strain:	*Oryzias latipes* (Orange-red killifish)
Exposure period:	48 Hours
Results:	LC_{50}: = 500 mg/L (48 hour)
Temperature:	No Data
Method:	Not given
Test Substance:	Methylhexahydrophthalic anhydride (unknown purity)
Analytical Monitoring:	Yes [X]; No [ ]; No Data [ ]
Remarks:	No other information was given.
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Reference:	Report summary cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992.

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

No Data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

No Data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rats
Value:	3300 mg/kg
Method:	Oral ingestion.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	No Data
Remarks:	No other data was supplied.
Reliability:	[2] Valid with restrictions
Reference:	Milliken Chemical Company, *Specialty Intermediates Pamphlet* AN-482-06 (9/96); Milliken Chemical Company, *Unpublished Report*, cited in MSDS No. 790773, January 17,2000.

(2) ACUTE INHALATION TOXICITY

No Data

(3) ACUTE DERMAL TOXICITY

No Data

B. REPEATED DOSE TOXICITY (General)

No Data

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

No Data

(2) NON-BACTERIAL *IN VITRO* TEST (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

No Data

(2) EYE IRRITATION/CORROSION

Specific studies were unavailable; however, in accordance with Directive 67/548/EEC, appropriate risk (R) phrases for MHHPA include: "Risk of Serious Damage to the Eyes".

B. SKIN SENSITIZATION

Specific studies were unavailable; however, in accordance with Directive 67/548/EEC, appropriate risk ® phrases for MHHPA include: "May cause sensitization by inhalation and skin contact."

C. RESPIRATORY SENSITIZATION

Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were found for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

C. RESPIRATORY SENSITIZATION (continued)

(a)

Method: Case report

Results: This article includes a case report of a woman who worked as a cleaner in a condenser factory. The condensers were filled with epoxy resin, a hardener, an accelerator and pigment. Approximately seven months after MHHPA was brought into use as the hardener, the worker came down with rhinitis and coughing. RASTs and prick tests for MHHPA-HAS(Human Serum Albumin Conjugates) were positive. Bronchial challenge with MHHPA was negative but the intense rhinitis evoked by the test confirmed occupational IgE mediated allergic rhinitis due to MHHPA. Positive prick test reactions indicated cross-reactivity between MHHPA-HAS and PA, maleic anhydride, trimellitic anhydride and MTHPA. RASTs to PA and MTHPA were also positive.

Reliability:

Remarks: Estimation or measurement of ambient air concentrations of MHHPA in the workplace were not given although occasional skin contact was noted.

Reference: Kanerva, L., et al., 1991

(b)

Method: Guinea pigs were immunized intradermally with a single dose of 0.3 M solution of MHHPA and other anhydrides. Specific IgE and IgG antibodies specific for guinea-pig serum albumin conjugates of the anhydrides were determined by passive cutaneous anaphylaxis (PCA) tests and enzyme-linked immunoabsorbant assay (ELISA).

Results: Specific IgG levels were increased in all animals immunized with MHHPA and specific IgE antibodies were positive.

Reliability:

Remarks: Product purity was $\geq$ 97%. Specific IgG, totals were analyzed by ELISA assay. PCA was used for analysis of IgE. The primary purpose of this article was to investigate structure activity relationships of organic acid anhydrides. The authors concluded that substitution of a hydrogen atom for a methyl group enhanced antibody formation. This substitution appeared to be the most marked general effect of chemical structure on immunogenicity.

Reference: Welinder, H., et al., 1995

7. REFERENCES

Dixie Chemical Company, Inc., *Material Safety Data Sheet for Methyl Hexahydrophthalic Anhydride (5/6/99)*

Grammer, L. C. et al., *Hemorrhagic Rhinitis – An Immunologic Disease due to Hexahydrophthalic Anhydride*, Chest 104(6):1792-1794, 1993

Grammer, L. C. et al., *Risk Factors for Immunologically Mediated Respiratory Disease from Hexahydrophthalic Anhydride*, J. Occup. Med. 36(6):642-646, 1994

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Kanerva, L. et al., *Delayed and Immediate Allergy caused by Methylhexahydrophthalic Anhydride*, Contact Dermatitis 36(1):34-38, 1997

Kanerva, L. et al., *Airborne Allergic Contact Urticaria from Methylhexahydrophthalic Anhydride and Hexahydrophthalic Anhydride* Contact Dermatitis 41(6):339-341, 1999

Klimisch, H. J., et al., *A systematic Approach for Evaluating the Quality of Experimental and Ecotoxicological Data,* Regulatory Toxicol. & Pharmacol. 25:1-5, 1997.

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Savolainen, H., and P. Pfaeffli. Acta Pharmacol. Toxicol. (Copenhagen) 59(3): 209-213, 1986

Welinder, H., *Specific Antibodies to Methyltetrahydrophthalic Anhydride in Exposed Workers*, Clin. Exp. Allergy 20(6):639-646, 1990

Welinder, H. and Nielsen, J., *Immunologic Tests of Specific Antibodies to Organic Acid Anhydrides*, Allergy 46:601-609, 1991

Welinder, H. E. et al., *Exposure-Response Relationships in the Formation of Specific Antibodies to Hexahydrophthalic Anhydride in Exposed Workers*, Scand. J. Work Environ. Health 20(6):459-465, 1994

Welinder, H., et al., *Structure-Activity Relationships of Organic Acid Anhydrides as Antigens in an Animal Model,* Toxicology 103:127-136, 1995

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 4

ROBUST SUMMARIES

FOR

METHYLTETRAHYDROPHTHALIC ANHYDRIDE
(34090-76-1)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

March, 2001

1. SUBSTANCE INFORMATION

CAS-Number 34090-76-1

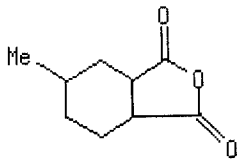
Name Methyltetrahydrophthalic Anhydride

Name Tetrahyro-5-methyl-1,3-Isobenzofurandione

EINECS-Number 251-823-9

Molecular Formula $C_9H_{10}O_3$

Structural Formula



Other Chemical Identity/Synonyms 4-Methyltetrahydrophthalic Anhydride; Tetrahydo-4-methylphthalic anhydride; MTHPA

Molecular Weight 166

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [X]; solid [ ]

Purity No Data

SYNONYMS Methyltetrahydrophthalic anhydride

IMPURITIES

No Data

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

No Data

B. BOILING POINT

(a)

Value:	> 585 °F
Pressure:	No Data
Decomposition:	No Data
Method:	ASTM D-86
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

(b)

Value:	283 °C
Pressure:	760 mm Hg
Decomposition:	No Data
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

C. VAPOUR PRESSURE

(a)

Value:	0.002 mm Hg
Temperature:	25 °C
Method:	calculated [X]; measured [ ]; ? [ ]
GLP:	Yes [ ] No [X] ? [ ]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

(b)

Value:	Negligible
Temperature:	16 ° C (60 ° F)
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

(c)

Value:	Negligible
Temperature:	60 °/100 ° F
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

D. PARTITION COEFFICIENT $log_{10}Pow$

No Data

E. WATER SOLUBILITY

Value:	No Data
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [ ]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	Slowly hydrolyzes to diacid in water.
Reference:	Lindau Chemical, MSDS for Lindride 12 (5/1/95)

F. pH Value, pKa Value

No Data

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Hydrolyzes to diacid.

C. BIODEGRADATION

No Data

D. TRANSPORT AND DISTRIBUTION

No Data

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

Type of Test:	Semi-static
Species/strain:	*Oryzias latipes* (Ricefish)
Exposure period:	96 Hours
Results:	LC_{50}: > 100 mg/L (96 hour)
Temperature:	No Data
Method:	"OECD Guidelines"
Test Substance:	Methyltetrahydrophthalic anhydride (unknown purity)
Analytical Monitoring:	Yes [ ]; No [ ]; No Data [X]
Remarks:	A semi-static system was used with renewal of water every 24 hours. No additional information available.
GLP:	Yes [X] No [ ] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	Office of Environmental Risk Assessment, Ministry of Environment, 1997.

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

Type of Test:	Static
Species/strain:	*Daphnia magna*
Exposure period:	48 Hours
Results:	EC_{50}= 130 mg/L (48 hours)
Temperature:	No Data
Method:	"OECD Guidelines"
Test Substance:	Methyltetrahydrophthalic anhydride (unknown purity)
Analytical Monitoring:	Yes [ ]; No [ ]; No Data [X]
Remarks:	No additional information available.
GLP:	Yes [X] No [ ] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	Office of Environmental Risk Assement, Ministry of Environment, Japan, 1997.

C. TOXICITY TO AQUATIC PLANTS - ALGAE

Type of Test:	Static – Growth inhibition
Species/strain:	*Selanastrum capricorn* (green algae)
Exposure period:	72 Hours
Results:	EC_{50}= 79 mg/L (72 hours) NOEC= 32 mg/L (72 hours)
Temperature:	No Data
Method:	"OECD Guidelines"
Test Substance:	Methyltetrahydrophthalic anhydride (unknown purity)
Analytical Monitoring:	Yes [ ]; No [ ]; No Data [X]
Remarks:	None
GLP:	Yes [X] No [ ] ? [ ]
Reliability:	[2] Valid with restrictions
Reference:	Office of Environmental Risk Assessment, Ministry of Environment, Japan, 1997.

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Crj:CD Rats
Value:	> 2000 mg/kg (for both males and females)
Method:	OECD Test Guideline 401
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Remarks:	Five (5) rats/sex were gavaged at 0, 500, 1000, or 2000 mg/kg of MTHPA in corn oil. Decreased birth weight, hypoactivity, shortness of breath and prone position were noted at 2000 mg/kg after 1 day. At necropsy, thickening, inflammation, adhesions, and squamous metaplasia of forestomach were seen at the two highest doses. No deaths occurred at any dose.
Reliability:	[1] valid without restrictions
Reference:	Safety Assessment Laboratory, Panapharm Laboratories Co., Ltc., 1285 Kurisaki-machi, Uto-shi, Kumamoto, 869-0, Japan, 1997.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley Derived Rats
Value:	3.69 ml/kg (~4.46 g/kg)
Method:	Groups of five male rats (205-275 g) were orally gavaged with undiluted material at dose levels of 0.464, 1.0, 2.15, 4.64 and 10 ml/kg. Animals were clinically observed for 14 days post-dosing. Gross autopsies were performed on all decedents and on all survivors at 14 days. This was an FHSA method (Code of Federal Regulations, Title 16, Chapter III, 1976).
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Undiluted liquid
Remarks:	The 95% confidence limits for this LD_{50} were 2.27-5.99 ml/kg. No deaths were seen at 0.464 or 1.0 ml/kg, 1 of 5 rats died at 2.15 ml/kg, 3 of 5 died at 4.64 ml/kg and 5 of 5 died at 10 ml/kg. At doses ≥ 2.15 ml/kg, clinical signs included hyperreactivity but no depression of bodyweight. Gross autopsy of decendents revealed gas and irritation in the intestinal tract and congestion of major organs. At 10 ml/kg, all deaths occurred within 24 hours. At other doses deaths occurred between 3 and 14 days. Gross autopsy on survivors was unremarkable.
Reliability:	[2] valid with restrictions
Reference:	Hill Top Research. *Unpublished Report* 78-645-21, July 25, 1978.

(c)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	2140 µl/kg (~2589 mg/kg)
Method:	Range Finding Study
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Details not reported except for 95% confidence limit (1480-3100 ml/kg).
Reliability:	[2] valid with restrictions
Reference:	H. F. Smyth. American Industrial Hygiene Association Journal 30:470, 1969; Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

(2) ACUTE INHALATION TOXICITY

No Data

(3) ACUTE DERMAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rabbit
Value:	1410 µl/kg (~1706 mg/kg)
Method:	No Data
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Details not reported
Reliability:	[2] valid with restrictions
Reference:	H.F. Smyth, 1969 Dixie Chemical Company, Inc., MSDS for ECA 100 (1/3/00)

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	>2000 mg/kg
Method:	Limit test; OCSE Linea Direttrice 402, 1987.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Remarks:	No details given.
Reliability:	[2] valid with restrictions
Reference:	Safephaun Laboratories Limited, U.K., 1987.

B. REPEATED DOSE TOXICITY (General)

Type:	Combined screening study to assess repeated dose toxicity, reproductive performance of male and female rats, and developmental toxicity potential.
Species/strain:	Crj:CD (SD) rats
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Oral gavage
Exposure period:	Males – 49 days; Females – 14 days before mating to day 3 of lactation (51 days). Terminal sacrifice of males occurred on day 50. Females were sacrificed on day 4 of lactation.
Frequency of treatment:	1 dose/day
Post exp. observation period:	None
Dose:	0, 30, 100, and 300 mg/kg/day in corn oil
Control group:	Yes [ ]; No [ ]; No Data [ ]; Concurrent no treatment [ ]; Concurrent vehicle [X]; Historical [ ]
NOEL:	Males – 30 mg/kg/day; Females – 100 mg/kg/day
LOEL:	Males – 100 mg/kg/day; Females – 300 mg/kg/day

B. REPEATED DOSE TOXICITY (continued)

Results:	MTHPA had no effect on body weight or food consumption at any dose level. The only adverse clinical sign was transient salivation in the 300 mg/kg groups. At termination, hematology was unremarkable in all groups but blood chemistry determinations showed decreased total cholesterol and BUN as well as increased triglycerides in males at 300 mg/kg. Upon autopsy, mucosal thickening of the forestomach in both sexes and increased adrenal weights in males were seen at the 300 mg/kg dose level. Histopathological examination revealed squamous metaplasia of the forestomach in males at 100 mg/kg and in both sexes at 300 mg/kg. Other forestomach changes seen at the 300 mg/kg dose included submucosal granulomatous inflammation, epithelial vacuolar change, edema, cellular infiltration and erosion. Other than suggestions of chronic irritation at the site of administration, no target organ for MTHPA was evident. The NOEL was reported to be 30 mg/kg in males and 100 mg/kg in females.
Method:	OECD Guideline No. 422: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X]; No [ ]; ? **[X]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Reliability:	[1] Valid without restriction
Reference:	Report from Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd., 1285 Kurisaki-machi, Uto-shi, Kumato, 869-04, Japan, 1997.

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

Type:	Bacterial reverse mutation assay (Ames test)
Species/strain:	*Salmonella typhimurium* bacteria (Strains TA 98, TA 100, TA 1535, and TA 1537)); *Escherichia coli* bacteria (WP 2)
Test System:	Pre-incubation method
Concentration:	62.5-2000 µg/plate for *S. typhimurium* without S9 activation; 156-5000 µg/plate for *E coli* without S9 activation; 313-5000 µg/plate for *S. typhimurium* and *E. coli* with S9 activation
Metabolic Activation:	With **[X]**; Without **[X]**
Results:	Non-mutagenic
Cytotoxic Concentration:	500 µg/plate for TA 1535; 1000 µg/plate for TA 100, TA 98, and TA 1537 without S9 activation; 2500 µg/plate for *E. coli* without S9 activation; 5000 µg/plate for TA 100 and TA 1537 with S9 activation
Precipitation:	Not applicable
Genotoxic Effects:	Negative in *E. coli* and all strains of *S. typhimurium* with and without metabolic (S9) activation
Method:	OECD Guidelines 471 and 472
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity by weight)
Remarks:	Four strains of *S. typhimurium* (TA 98, TA 100, TA 1535, and TA 1537) and one strain of *E. coli* (WP2) were tested using a pre-incubation method. Three culture plates and two replicates were used at each dose level in both the presence and absence of a S9 rat liver homogenate. Appropriate positive controls were used with S9 (2AA) and without S9 (AF2, 9AA, SA) activation.
Reliability:	[1] Valid without restrictions.
Reference:	Hatano Research Institute Report, Food and Drug Safety Center, 729-5 Ochai, Hadano-shi, Kanagawa, 257, Japan, 1997.

(2) NON-BACTERIAL IN VITRO TEST (chromosome aberration)

Type:	Cytogenetic assay (chromosomal aberration)
Species/strain:	Chinese Hamster Lung (CHL/IU) cells
Test System:	Chinese Hamster Lung
Concentration:	Continuous treatment without S9 activation – 0, 0.075, 0.15, and 0.30 mg/ml; Short-term treatment without S9 activation – 0, 0.05, 0.10 and 0.20 mg/ml; Short-term treatment with S9 activation – 0, 0.11, 0.21, and 0.43 mg/ml.
Metabolic Activation:	With **[X]**; Without **[X]**
Results:	Negative for chromosomal aberration. Equivocal for polyploidy.
Cytotoxic Concentration:	Unknown
Precipitation:	Not applicable
Genotoxic Effects:	Structural chromosomal aberrations were not induced following 24 hours of continuous treatment. Polyploidy (1.13-1.88%) was weakly induced at 0.3 mg/ml without S9 activation after 48 hours of continuous treatment and at all concentrations (0.11-0.43 mg/ml) with short -term treatment and S9 activation.
Method:	OECD Guideline 473
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity by weight)
Remarks:	The maximum dose tested is a concentration of the test substance that produces a 50% or greater inhibition of cell growth or mitosis. Several lower graded dose levels were also used. Two culture plates/dose level were used and S-9 was prepared from rat liver induced with phenobarbital and 5,6-benzoflavone.
Reliability:	[1] Valid without restrictions.
Reference:	Hatano Research Institute Report, Food and Drug Safety Center, 729-5 Ochai, Hadano-shi, Kanagawa, 257, Japan, 1997.

D. REPRODUCTIVE TOXICITY

Type:	Combined screening study to assess repeated dose toxicity, reproductive performance of male and female rats, and developmental toxicity potential.
Species/strain:	Crj:CD (SD) rats
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Oral gavage
Exposure period:	Males – 49 days; Females – 14 days before mating to day 3 of lactation (51 days). Terminal sacrifice of males occurred on day 50. Females were sacrificed on day 4 of lactation.
Frequency of treatment:	1 dose/day
Post exp. observation period:	None
Dose:	0, 30, 100, and 300 mg/kg/day in corn oil
Control group:	Yes [ ]; No [ ]; No Data [ ]; Concurrent no treatment [ ]; Concurrent vehicle **[X]**; Historical [ ]
NOEL:	Males/Females – 300 mg/kg/day
LOEL:	Males/Females - > 300 mg/kg/day
Results:	No effects were observed on estrous cycle, numbers of corporeal lutea and implantations, copulation index, or fertility indices. Examination at delivery and during the lactation period showed no effects on the length of gestation, litter size, live newborns, gestational, stillborn and birth indices, sex ratio, body weight of offspring at birth and at day 4 after birth, or viability index on day 4. No external anomalies were apparent. The NOEL from this screening study was greater than 300 mg/kg for male and female reproductive performance and for developmental toxicity.

D. REPRODUCTIVE TOXICITY (continued)

Method:	OECD Guideline No. 422: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X]; No [ ]; ? **[X]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Reliability:	[1] Valid without restriction
Reference:	Report from Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd., 1285 Kurisaki-machi, Uto-shi, Kumato, 869-04, Japan, 1997

E. DEVELOPMENTAL TOXICITY

Type:	Combined screening study to assess repeated dose toxicity, reproductive performance of male and female rats, and developmental toxicity potential.
Species/strain:	Crj:CD (SD) rats
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Oral gavage
Exposure period:	Males – 49 days; Females – 14 days before mating to day 3 of lactation (51 days). Terminal sacrifice of males occurred on day 50. Females were sacrificed on day 4 of lactation.
Frequency of treatment:	1dose/day
Post exp. observation period:	None
Dose:	0, 30, 100, and 300 mg/kg/day in corn oil
Control group:	Yes [ ]; No [ ]; No Data [ ]; Concurrent no treatment [ ]; Concurrent vehicle **[X]**; Historical [ ]
NOEL:	Males/Females – 300 mg/kg/day
LOEL:	No Data
Results:	No effects were observed on estrous cycle, numbers of corporeal lutea and implantations, copulation index, or fertility indices. Examination at delivery and during the lactation period showed no effects on the length of gestation, litter size, live newborns, gestational, stillborn and birth indices, sex ratio, body weight of offspring at birth and at day 4 after birth, or viability index on day 4. No external anomalies were apparent. The NOEL from this screening study was greater than 300 mg/kg for male and female reproductive performance and for developmental toxicity.
Method:	OECD Guideline No. 422: Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
GLP:	Yes [X]; No [ ]; ? **[X]**
Test substance:	Methyltetrahydrophthalic anhydride (99.97% purity)
Reliability:	[1] Valid without restriction
Reference:	Report from Safety Assessment Laboratory, Panapharm Laboratories Co., Ltd., 1285 Kurisaki-machi, Uto-shi, Kumato, 869-04, Japan, 1997

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

Type of Test:	Primary Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating **[X]**; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating **[X]**; Not irritating [ ]
Method:	Draize test
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Score of 1 on a 10 point scale. Classified as irritating in accordance with EC Directive 67/548/EEC. No other details.
Reliability:	[2] valid with restrictions
Reference:	H.F. Smyth, 1969.

(2) EYE IRRITATION/CORROSION

Type of Test:	Primary Eye Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating **[X]**; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes **[X]**
Method:	Draize test
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	No Data
Remarks:	Score of 9 on a 10 point scale. Classified as irritating in accordance with EC Directive 67/548/EEC.
Reliability:	[2] valid with restrictions
Reference:	H.F. Smyth, 1969.

B. SKIN SENSITIZATION

Specific studies were unavailable; however, in accordance with Directive 67/548/EEC, appropriate risk ® phrases for MHHPA include: "May cause sensitization by inhalation and skin contact."

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were located for NMA. Symptoms of over-exposure include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

B. RESPIRATORY SENSITIZATION (continued)

(a)

Method: A group of 145 workers exposed to MTHPA was investigated. The group was divided into three different exposure categories according to their contact with the epoxy resin. The average exposure levels at the time of the investigation were: 0.085 mg/m^3 (Zone I), 0.014 mg/m^3 (Zone II), and 0.010 mg/m^3 (Zone III) though the exposure was probably higher earlier.

Results: Specific IgE antibodies (RAST) to a conjugate between MTHPA and human serum albumin (HAS) were statistically significantly increased (P = 0.001; 26 subjects = 18% positive) in the exposed group, compared to a non-exposed control group (n = 33). Twenty-three exposed subjects were also skin-prick test positive to MTHPA-HAS. There was an association between exposure intensity and RAST-positive persons. The authors conclude that MTHPA is a sensitizing agent at low levels of exposure.

Reliability: [2] Valid with restrictions

Remarks: One worker positive to specific IgE antibodies to a conjugate between MTHPA and human serum albumin was only exposed for 2 months. Forty-four persons (30%) were smokers, and 16 (11%) atopics.

Reference: Welinder, et al., 1990

(b)

Method: In this case study, a 22 year old non-smoking male exhibited work-associated rhinitis and asthma. Bronchial hyperreactivity following provacation with methacholine, skin prick test positivity and specific immunoglobulin E (IgE) serum antibodies agains a MTHPA conjugate were noted.

Results: The disease appeared to be caused by an IgE-mediated allergy to MTHPA.

Reliability: [2] Valid with restrictions

Remarks: The patient had a heredity of rhinitis. About 4 months after beginning a job which involved working with MTHPA and methyl imidazole, he experienced nasal secretion and congestion during work. Some time later, he developed chest tightness, a continual productive cough and occasional wheezing. A skin prick test was positive to a conjugate of MTHPA and human serum albumin (HAS). None of the 34 unexposed reference workers in a nearby factory were positive to MTHPOA-HAS. The total immunoglobulin (Ig)E level was 235 kU/I. In the radioallergosorbent test (RAST), specific IgE antibodies to MTHPA-HAS were found (RAST ratio 7.5). In the enzyme-linked immunosorbent assay (ELISA), specific IgG antibodies were not present (optical density 0.32). Sera from 30 referents had a median total IgE of 11 (range 1-127) kU/I. When tested with MTHPA-HAS, the referents' RAST ratio for IgE was 1.1 (range 0.7-2.0), and their ELISA value for specific IgG was 0.04 (range 0-0.4) in optical density. After a period of vacation, he was removed from exposure to MTHPA. Symptoms gradually disappeared during the next five weeks. The day before a second examination, he was once more exposed to MTHPA at his work site. After about 2 H of exposure, he suffered from nasal congestion and irritation. The time weighted MTHPA exposure at the original job site was 0.1 mg/m^3.

Reference: Nielsen, J., et al., 1989

(c)

Method: In this case study, a patient positive to a prick test with MTHPA-HAS and specific IgE determination (who had been occupationally exposed to MTHPA) underwent a bronchial provocation test to cold MTHPA, heated MTHPA, and a placebo.

Reliability: [2] Valid with restrictions

Results: The bronchial provocation test with the placebo and cold MTHPA (0.2 mg/m^3) were negative. The bronchial provocation test to MTHPA heated to workroom temperature (100 °C) was positive. The MTHPA concentration in the chamber air was 7 mg/m^3 during the 30 minute provocation test. Wheezing and rales were induced after 6 H. After six months without exposure, the patient had fewer symptoms. The patient was diagnosed with probable occupational asthma caused from sensitization to MTHPA.

Reference: Kanerva, L., et al., 1991

6. REFERENCES

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HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

APPENDIX 5

ROBUST SUMMARIES

FOR

NADIC METHYL ANHYDRIDE
(25134-21-8)

Submitted to the U.S. EPA

By

The Industrial Health Foundation, Inc. Cyclic Anhydride Committee

Consortium Registration Number:

March, 2001

CONTENTS

1. SUBSTANCE INFORMATION

CAS-Number 25134-21-8

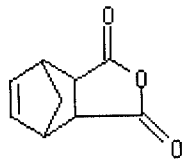
Name Nadic Methyl Anhydride

Name 5-Norbornene-2,3-Dicarboxylic Anhydride, Methyl-; Methyl-5-norbornene-2,3-dicarboxylic; 4,7-Methanoisobenzofuran-1,3-dione,3a,4,7,7a-tetrahydromethyl; Methylbicyclo (2,2,1) hept-5-ene-2,3-dicarboxylic anhydride; Nadic Methyl Anhydride; NMA

EINECS-Number 2466448

Molecular Formula $C_{10}H_{10}O_3$

Structural Formula



D1—Me

Other Chemical Identity/Synonyms Methyl-5-norbornene-2,3-dicarboxylic anhydride; 4,7-Methanoisobenzofuran-1,3-dione,3a,4,7,7a -tetrahydromethyl; Methylbicyclo (2,2,1) hept-5-ene-2,3-dicarboxylic anhydride; Nadic Methyl Anhydride; NMA

Molecular Weight 178.2

Type of Substance

element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

Physical State *(at 20°C and 1.013 hPa)*

gaseous [ ]; liquid [X]; solid [ ]

Purity 99% weight/weight

SYNONYMS Bicyclo (2,2,1) Hept-5-ene-2,3-Dicarboxylic Anhydride, Methyl; 5-Norbornene-2,3-Dicarboxylic Anhydride,Methyl-; 4,7-Methanoisobenzofuran-1,3-dione,3a,4,7,7a-tetrahydromethyl; Nadic Methyl Anhydride; NMA

IMPURITIES

CAS No:	Not Found
EINECS No:	Not Listed
Name:	Free Acid
Value:	1% (maximum weight/weight)

2. PHYSICAL-CHEMICAL DATA

A. MELTING POINT

Value:	<18 °C
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Sublimation:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	Becomes "glassy"
Reference:	Buffalo Color Corporation, 12/95; Buffalo Color Corporation, *MSDS 127-2641* (12/8/97)

B. BOILING POINT

Value:	140 °C (Approximate)
Pressure:	10 mm Hg
Decomposition:	Yes [ ] No [X] Ambiguous [ ]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2641 (12/8/97); Lonza Inc./Lonza Spa, NMA MSDS, 12/14/98

C. VAPOR PRESSURE

(a)

Value:	1.5 mm Hg
Temperature:	30 °C
Method:	calculated [ ]; measured [ ] ? [X] No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Estimated
Reference:	Buffalo Color Corporation, Technical Bulletin, "Anhydrides"

(b)

Value:	5.0 mm Hg
Temperature:	120 °C
Method:	calculated [ ]; measured [ ] ? [X] No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	None
Reference:	Buffalo Color Corporation, MSDS 127-2641 (12/8/97); Lonza Inc./Lonza Spa, NMA MSDS, 12/14/98

C. **VAPOR PRESSURE (continued)**

(c)

Value:	0.1 mm Hg
Temperature:	20 °C
Method:	calculated [ ]; measured [ ] ? [X]
	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Approximate
Reference:	Buffalo Color Corporation, Technical Bulletin, "Anhydrides"

D. **PARTITION COEFFICIENT $\log_{10}$Pow**

Log_{10} Pow:	1.35 ± 0.03
Temperature:	No Data
Method:	calculated [ ]; measured [ ] ? [X]
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[4] Not assignable
Remarks:	Octanol/Water Partition Coefficient, P = 22.4
Reference:	Fuhr, A.B./J.A. Gouck, 1980 (memo); Buffalo Color Corporation, MSDS 127-2641 (12/8/97)

E. **WATER SOLUBILITY**

Value:	Insoluble
Temperature:	No Data
Description:	Miscible[ ]; Of very high solubility [ ]; Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]; Of low solubility [X]; Of very low solubility [ ]; Not soluble [X]
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] Valid with restrictions
Remarks:	Insoluble in water, but will hydrolyze to diacid in presence of water or and cold acid (pH = 5). Hydrolyzes and forms dibasic salt in cold alkalis (pH=9). Soluble in toluene, acetone, benzene, naptha, and xylene. Probably soluble in $CHCl_3$, 1,1,1-Trichloroethylene, ether and cyclohexane.
Reference:	Buffalo Color Corporation, 12/95; Buffalo Color Corporation, MSDS 127-2641 (12/8/97)

F. **pH Value, pKa Value**

pH Value:	2.4
Concentration:	10% aqueous solution
Temperature:	No Data
Method:	No Data
GLP:	Yes [X] No [ ] ? [ ]
pKa value	Not Given
Reliability:	[4] Not assignable
Remarks:	pH of diacid estimated at approximately 4 by analogy to HHPAA
Reference:	FDRL Report of Study 6771F, February 27, 1981.

3. ENVIRONMENTAL FATE AND PATHWAYS

A. PHOTODEGRADATION

No Data

B. STABILITY IN WATER

Not Stable – Will hydrolyze to diacid.

C. BIODEGRADATION

(a)

Type:	Aerobic **[X]**; Anaerobic **[ ]**
Inoculum:	Activated Sludge
Concentration:	10 mg/L (test substance)
Medium:	No Data
Degradation:	0.0 %
Kinetics:	No Data
Method:	OECD Guideline 303A
Test Substance:	Nadic methyl anhydride (Purity unknown)
Results:	Zero percent biodegradation as measured by BOD. Approximately 1.0% biodegradation as measured by TOC. NMA was hydrolyzed to the corresponding acid in the three replicate tests conducted.
Test Conditions:	The test substance concentration was 100 mg/L. The activated sludge concentration as the concentration of suspended solid was 30 mg/L. The volume of the test solution was 300 ml. Cultivation temperature was constant at 25 °C for the 28 day duration.
GLP:	Yes [X] No **[ ]** ? **[ ]**
Reliability:	[2] Valid with restrictions
Remarks:	Biochemical Oxygen Demand (BOD) was determined and Total Organic Carbon (TOC) was analyzed.
Reference:	Report summary cited by the Japan Chemical Industry Ecology-Toxicology Information Center, October, 1992

(b)

Type:	Calculated ThOD
Value:	ThOD = 1.89 g O_2/g
Method:	No Data – Calculated.
GLP:	Yes **[ ]** No **[ ]** ? **[X]**
Reliability:	[4] Not assignable
Remarks:	None
Reference:	Buffalo Color Corp., 12/95

4. ECOTOXICITY

A. ACUTE/PROLONGED TOXICITY TO FISH

No Data

B. ACUTE TOXICITY TO AQUATIC INVERTEBRATES - DAPHNIA

No Data

C. TOXICITY TO AQUATIC PLANTS - ALGAE

No Data

5. TOXICITY

A. ACUTE TOXICITY

(1) ACUTE ORAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Sprague-Dawley Rats - Female and Male
Value:	958 mg/kg (856-1077 CL)
Method:	Single undiluted oral dose was administered to 5 rats/sex/dose at doses of 650, 801, 987, 1217 and 1530 mg/kg. OECD Study.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	Undiluted liquid
Reliability:	[1] Valid without restrictions.
Remarks:	Mortality occurred at all dose levels: One (1) of 5 males and 0 of 5 females at 650 mg/kg; 1 of 5 males and 1 of 5 females at 801 mg/kg; 2 of 5 males and 2 of 5 females at 987 mg/kg; 5 of 5 males and 4 of 5 females at 1217 mg/kg; 5 of 5 males and 5 of 5 females at 1530 mg/kg. All deaths occurred within 6 days post-dosing. Clinical signs in those rats that died included weight loss, blood in urine, and decreased activity. Survivors gained weight normally. Necropsy findings in decedents included dark lungs and blood-like fluid in the intestines.
Reference:	Food and Drug Research Laboratories, Study No. 6771F, 1/20/81.

(b)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} [X]; LDL_0 [ ]; Other [ ]
Species/strain:	Rat
Value:	914 mg/kg
Method:	No Data
GLP:	Yes [ ] No [ ] ? [X]
Test Substance:	No Data
Reliability:	[4] Not assignable
Remarks:	Limited data available. Details of toxic effects not reported.
Reference:	NIOSH/RTECS, April 1989, RB 91000

(2) ACUTE INHALATION TOXICITY

Type:	LC_0 [ ]; LC_{100} [ ]; LC_{50} [ ]; LCL_0 [ ]; Other [X]
Species/strain:	Sprague-Dawley Rats – Female and Male
Exposure time:	4 hours
Value:	750 mg/m^3 (aerosol), lethal level
Method:	Modified OECD Limit Test. Five(5) rats/sex were exposed to an aerosol of NMA for 4 hours and observed for 14 days. Toxic signs and body weights were taken periodically and gross autopsies were conducted at termination.
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	90% NMA in ethyl alcohol
Reliability:	[2] valid with restrictions.

(2) ACUTE INHALATION TOXICITY (continued)

Remarks:	Aerosol concentration was determined gravimetrically. Geometric mean particle size was 3.2 μm with a GSD of 2.1. Ninety-three percent (93%) of particles were less than 10 μm. Three (3) of five males and 5 of 5 females died between 3 and 7 days post-dosing. Toxic signs included labored breathing, nasal discharge, urinary incontinence and bloody urine, cloudy eyes and weight loss. Gross autopsy showed pale organs related to vascular congestion. A parallel study with an ethyl alcohol aerosol produced no effects.
Reference:	Food and Drug Research Laboratories, Study No. 6771F, 3/24/81.

(3) ACUTE DERMAL TOXICITY

(a)

Type:	LD_0 [ ]; LD_{100} [ ]; LD_{50} **[X]**; LDL_0 [ ]; Other [ ]
Species/strain:	Ti_FRAI_f rats
Value:	4920 mg/kg (3670-6590 CL)
Method:	NMA was applied dermally at doses of 2000, 3000, 4000 and 5000 mg/kg for 24 hours and rats were observed for 14 days post-dosing. Five (5) males and 5 females were used at each dose. Clinical signs and body weights were periodically monitored. At termination of dosing, at 24 hours and periodically thereafter, the skin was carefully examined for adverse reactions.
GLP:	Yes [ ] No [ ] ? **[X]**
Test substance:	No Data
Reliability:	[2] valid with restrictions.
Remarks:	Mortality was: 0 of 5 M and 0 of 5 F at 2000 mg/kg; 1 of 5 M and 1 of 5 F at 3000 mg/kg; 2 of 5 M and 1 of 5 F at 4000 mg/kg; and 2 of 5 M and 3 of 5 F at 5000 mg/kg. Clinical signs included a reduction in spontaneous motility, ataxia, eyelid closure, dulled response to pain, and irregular respiration (disappeared in survivors by 5 days post-dosing). On the basis of skin reactions, the authors called NMA a mild skin irritant.
Reference:	CIBA-Geigy Laboratory, 9/27/77.

(b)

Type:	LD_0 **[X]**; LD_{100} [ ]; LD_{50} [ ]; LDL_0 [ ]; Other [ ]
Species/strain:	New Zealand albino rabbits – male and female
Value:	> 2000 mg/kg.
Method:	Modification of OECD Limit Test. A single dose (2000 mg/kg) was given dermally to 5 male and 5 female rabbits, allowed to stay on the skin for 24 hours, and the animals were then observed for 14 days post-dosing. Clinical signs and body weights were monitored periodically and gross autopsies were performed upon termination.
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	Undiluted NMA
Reliability:	[2] valid with restrictions.
Remarks:	All rabbits survived and gained weight through 14 days post-dosing. Clinical signs included slight nasal discharge and loss of appetite. Mild skin irritation was noted on several occasions. Necropsies were unremarkable.
Reference:	Food and Drug Research Laboratories, Study No. 6771F, 3/21/81.

B. REPEATED DOSE TOXICITY (General)

No Data

C. GENETIC TOXICITY IN VITRO

(1) BACTERIAL

No Data

(2) NON-BACTERIAL *IN VITRO TEST* (CHROMOSOME ABERRATION)

No Data

D. REPRODUCTIVE TOXICITY

No Data

E. DEVELOPMENTAL TOXICITY

No Data

6. TOXICOLOGICAL INFORMATION CHARACTERISTIC FOR CYCLIC ANHYDRIDE CATEGORY

A. CORROSIVENESS/IRRITATION

(1) SKIN IRRITATION/CORROSION

(a)

Type of Test:	Primary Irritation
Species/strain:	New Zealand albino rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderately irritating [ ]; Slightly irritating [X]; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]
Method:	Draize Test (Modification of OECD test)
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	On a scale of 8, a 50% suspension in PEG 400 was scored 0.75. No irritation was seen at a concentration of 6.5%
Reference:	FDRL Report of Study 6771-F, 3/5/82.

(b)

Type of Test:	Primary Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderately irritating [X]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Highly corrosive (causes severe burns) [ ]; Corrosive (caused burns) [ ]; Irritating [X]; Not irritating [ ]
Method:	Draize Test (Modification of OECD Test)
GLP:	Yes [X] No [ ] ? [ ]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	Undiluted NMA was scored 3.9 on a scale of 8.
Reference:	FDRL Report of Study 6771-F, 3/5/82.

(2) EYE IRRITATION/CORROSION

(a)

Type of Test:	Acute Eye Irritation
Species/strain:	New Zealand albino rabbit
Results:	Highly corrosive **[X]**; Corrosive [ ]; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes **[X]**
Method:	Draize Test
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No wash. 83 on scale of 110 at 72 hours.
Reference:	FDRL Report of Study 6771-F, 2/27/81.

(b)

Type of Test:	Acute Eye Irritation
Species/strain:	New Zealand albino rabbit
Results:	Highly corrosive [ ]; Corrosive [ ]; Highly irritating [ ]; Irritating **[X]**; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes **[X]**
Method:	Draize Test
GLP:	Yes **[X]** No [ ] ? [ ]
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	4 second washout. 12-37 on scale of 110 at 72 H.
Reference:	FDRL Report of Study 6771-F, 3/21/81

(c)

Type of Test:	Acute Eye Irritation
Species/strain:	Rabbit
Results:	Highly corrosive [ ]; Corrosive **[X]**; Highly irritating [ ]; Irritating [ ]; Moderate irritating [ ]; Slightly irritating [ ]; Not irritating [ ]
Classification:	Irritating [ ]; Not irritating [ ]; Risk of serious damage to eyes **[X]**
Method:	Draize Test
GLP:	Yes [ ] No [ ] ? **[X]**
Test substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	No wash. 67 on scale of 110 at 72 H.
Reference:	Ferber, K.H./J.F. Best (letter), 10/10/66

B. SKIN SENSITIZATION

Type:	
Species/Strain:	Human
Results:	Sensitizing **[X]**; Not sensitizing [ ]; Ambiguous [ ]
Classification:	Sensitizing **[X]**; Not sensitizing [ ]
Method:	Sensitization Patch Test
Test Substance:	No Data
Reliability:	[2] Valid with restrictions
Remarks:	Thirty four (34) out of 53 human subjects showed skin reactions during induction and at challenge indicating positive evidence of sensitization.
Reference:	FDRL, 5/7/82.

C. RESPIRATORY SENSITIZATION

Note: Organic acid anhydrides in general are low molecular weight, reactive molecules that have been associated with mucosal irritation, skin and respiratory sensitization, severe eye irritation and mild to moderate skin irritation. Some of these compounds are corrosive to the eyes. Sensitization has been noted in various studies on both humans and animals; however, no studies were for NMA. By analogy to other acid anhydrides, NMA would be expected to cause respiratory sensitization. Industrial medical surveillance has indicated that NMA causes respiratory sensitization. Symptoms of over-exposure may include rhinitis, conjunctivitis and asthma-like effects. Specific serum IgE and IgG antibodies to a fairly large number of anhydrides have been found in exposed workers.

References: Grammer, et. al, 1994 and 1995 (HHPA); Kanerva, et al., 1997 and 1997; Welinder, 1991 (MHHPA) Welinder, et al., 1990 and 1994 (MTHPA); Buffalo Color Corporation, 1995 (NMA)

Type:	Industrial/Medical Surveillance
Results:	Source: Buffalo Color Corporation A number of customers have advised of complaints of asthmatic reactions to inhaled NMA. Manufacturers have less trouble in this regard probably because of better enclosure and ventilation. Transient eye and lung irritation have occasionally been reported.
Remarks:	Manufactured by Buffalo Color Corporation for a number of years without serious or lasting effects. No special medical surveillance to date. Personal and area monitoring data based on TOC of dust samples as of 1987 indicate compliance with BCC LV and CV with some exceptions. No epidemiology.
Reference:	Buffalo Color Corporation, 12/95

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